# Does Perchlorate in Drinking Water Affect Thyroid Function in Newborns or School-Age Children?

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*Perchlorate is known to suppress thyroid function by inhibiting uptake of iodide by the human thyroid at doses of 200 mg/day or greater. A study was conducted to investigate the potential effects of perchlorate in drinking water on thyroid function in newborns and school-age children. A total of 162 school-age children and 9784 newborns were studied in three proximate cities in northern Chile that have different concentrations of perchlorate in drinking water: Taltal (100 to 120 μg/L), Chañaral (5 to 7 μg/L), and Antofagasta (non-detectable: <4 μg/L). Among schoolchildren, no difference was found in thyroid-stimulating hormone levels or goiter prevalence among lifelong residents of Taltal or Chañaral compared with those of Antofagasta, after adjusting for age, sex, and urinary iodine. No presumptive cases of congenital hypothyroidism were detected in Taltal or Chañaral; seven cases were detected in Antofagasta. Neonatal thyroid-stimulating hormone levels were significantly lower in Taltal compared with Antofagasta; this is opposite to the known pharmacological effect of perchlorate, and the magnitude of difference did not seem to be clinically significant. These findings do not support the hypothesis that perchlorate in drinking water at concentrations as high as 100 to 120 μg/L suppresses thyroid function in newborns or school-age children.*

Perchlorate salts have been used as oxidizing components in solid propellants for rockets, missiles, and fireworks for over 50 years. In 1952, perchlorate was shown to suppress thyroid function at doses of 200 mg/day or greater by reversibly inhibiting uptake of iodide into the thyroid gland.[1,2] It is currently used medically to treat hyperthyroidism of various etiologies at doses of up to 900 mg/day.

In 1985, perchlorate associated with aerospace industrial operations was thought to be detected in groundwater in the western United States but was not confirmed.[3] The detection limit before March 1997 was 400 μg/L and thereafter was 4 μg/L.[4] Use of the improved analytical method led to the detection of perchlorate in the range of 4 to 200 μg/L in numerous groundwater sources in California, Nevada, and Utah.[5] Perchlorate was detected at concentrations of 4 to 16 μg/L in Lake Mead and the downstream Colorado River.[3] At that time, there were no health effect studies of chronic low dose exposure to perchlorate in humans.

In 1997 and 1998, two cross-sectional occupational health studies were conducted at the two perchlorate producing facilities in the United States.[6,7] Exposed workers in these studies were healthy adults, and exposure was through the respiratory route. The exposure–dose relationship was well documented by correlating urinary perchlorate excretion to airborne particulate perchlorate

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levels.[7] These studies found no indication of thyroid or other adverse health effects from chronic occupational perchlorate exposure. The group of individuals exposed to the highest concentrations of perchlorate absorbed an average of 34 mg/day and exhibited no effects on thyroid function.

Because normal thyroid function is necessary for normal neurological development, it has been postulated that the developing fetus and newborn are the most sensitive subpopulations. Two epidemiological studies[8,9] were recently completed that used neonatal screening data from state health departments in California and Nevada. These studies found no increase in incidence of congenital hypothyroidism, nor decrease in neonatal thyroxine (T4) levels, associated with environmental perchlorate concentrations of up to 15 μg/L.

To date, most documented detections of perchlorate in US water sources are believed to be of relatively recent origin and to be associated with the defense and rocket industries. However, a recent report[10] suggests that perchlorate is present in fertilizer from a number of sources. For nearly a century, perchlorate has been known to be present in Chilean nitrate fertilizer in concentrations ranging from 0.5 mg/kg to greater than 60 mg/kg.[11-18]

Nitrates have been mined in the Atacama Desert of northern Chile and exported to North America and Europe for use in gunpowder and fertilizer beginning more than 200 years ago.[15] The nitrate deposits contain unusually highly oxidized saline constituents including nitrate, iodate, perchlorate, and chromate. The Atacama Desert is one of the most arid regions on Earth, with measurable rainfall (>1 mm) occurring locally as infrequently as once in 5 to 20 years. Nevertheless, the Atacama Desert has widespread and abundant groundwater that is recharged by infiltration from infrequent stream flow and by slow groundwater movement from the high Andes Mountains.[18] Some of the drinking water supply in northern Chile is obtained from water wells that tap this groundwater; other important water supplies are obtained from the western margin of the Andes.

Thyroid disease has been well studied and characterized in Chile over the past 20 to 30 years.[19-27] Historically, goiter has been endemic in Chile with a prevalence of approximately 40%, using World Health Organization criteria.[28] With the introduction of iodized salt in 1982, prevalence of goiter dropped to about 10%. In 1992, the Chilean Ministry of Health initiated a neonatal thyroid screening program throughout the country.

The present study was conducted to investigate the hypothesis that perchlorate in drinking water suppresses thyroid function in newborns and school-age children, as demonstrated by increased thyroid-stimulating hormone (TSH) or decreased free thyroxine (free T4) levels. An additional purpose of this study was to assess the feasibility of conducting future studies in northern Chile to further define possible relationships between perchlorate in drinking water and thyroid function.

## Preliminary Water Surveys for Perchlorate

In December 1998, samples for laboratory chemical analysis were obtained by Errol L. Montgomery & Associates, Inc (Tucson, AZ) from water sources in the Atacama Desert in proximity to known nitrate deposits. Perchlorate concentrations of 1000 to 10,000 μg/L were detected in groundwater samples from sources reportedly used exclusively for industrial purposes. Groundwater used for metallurgical processes at a copper mine between Antofagasta and Calama is treated with reverse osmosis to control perchlorate levels, and concentrations are monitored daily. One natural spring used recreationally was found to have perchlorate concentrations of about 1000 μg/L.

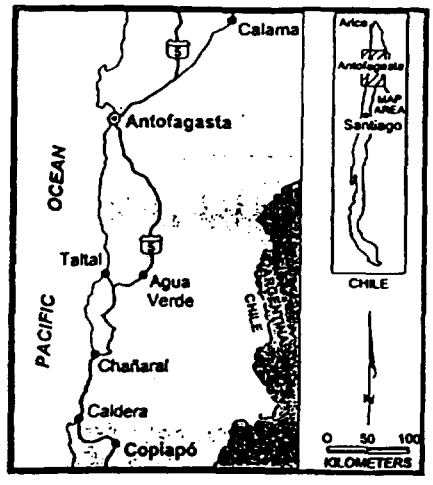


Fig. 1. Study locations in northern Chile.

Perchlorate concentrations in the range of 50 to 150 μg/L were detected in groundwater used for human consumption. In particular, a well field at Agua Verde that supplies municipal water to the city of Taltal had perchlorate detectable in excess of 100 μg/L (see Fig. 1 for study locations). Perchlorate was not detectable in samples taken from the Rio Loa, one of the few flowing streams in the Atacama Desert.

In April 1999, samples of municipal water for the largest coastal cities along the northern 1200 km in Chile (Arica, Pisagua, Iquique, Tocopilla, Antofagasta, Taltal, Chañaral, Caldera, and Copiapo) were obtained. In this second survey, water samples were obtained from three residences in each city, and the source of potable water was determined.

Antofagasta and Tocopilla obtain potable water through a pipeline from sources in the western margin of the Andes Mountains near Calama, 200 km to the northeast from Antofagasta. Perchlorate was not detectable in water samples obtained from either of these two cities. The principal source of potable water for all other cities surveyed is groundwater from wells in alluvial basins west of the Andes Mountains. Per-

chlorate was detected in tap water from Arica, Pisagua, Iquique, Chañaral, Caldera, and Copiapo in the range of 4 to 12 μg/L. For Chañaral, the source of potable water is reported to consist of five water wells located in Copiapo. The water is pumped to a storage tank and transported by means of gravity through a pipeline to Chañaral.

Perchlorate was detected in tap water from Taltal in the range of 110 to 120 μg/L. Taltal receives its municipal water through a pipeline from a well field located near Agua Verde, about 45 km east of the city. At Agua Verde, groundwater is pumped from five wells, four of which were completed in 1971 and one in 1997. The wells are drilled and cased, with depths ranging from about 220 meters to as deep as 344 meters in alluvial deposits. These five wells replaced shallow hand-dug wells in the same area with detectable perchlorate of up to 250 μg/L that previously supplied water to Taltal. Water for Taltal is reportedly obtained from aquifers in the Agua Verde area from about 1900 to the present.

## Methods

This study was conducted in September 1999. All research activities and a subject consent form (for participation of schoolchildren) were approved in advance by the review board of the Southeast Metropolitan Health Service in Santiago, Chile.

## Subject Selection

Taltal (population 12,000) was selected as the primary study city because it had the highest perchlorate concentrations detected in drinking water in preliminary surveys. Antofagasta (population 150,000), about 200 km to the north, was selected as a control city because perchlorate was undetectable in samples of municipal water. Chañaral (population 20,000) was selected as a third study city because of its proximity to Taltal (about 100 km to the south), similar size and economy, and because perchlorate concentrations in drinking water are similar to those in some water sources in the southwestern United States (about 7 μg/L).[3]

One or two public schools in Antofagasta, Chañaral, and Taltal were invited to participate in the study. At each participating school, all first- and second-grade students (50 to 60 per city) were given a consent form and questionnaire to be taken home, completed by parents, and returned. More than 90% of these students in each city participated fully in the study. These children ($n$ = 163) were from 6 to 8 years of age, of similar ethnicity (parents of predominantly Spanish origin), and had similar socioeconomic characteristics typical to this region. The questionnaire ascertained the children's contact information, date and town of birth, residence history, mother's residence for the year preceding the child's birth, nutrition during the first 6 months of life, current medications, parents' occupation, and family history of thyroid disease.

Neonatal thyroid screening records were obtained for all neonates born between February 1996 and January 1999 and whose city of origin was Antofagasta, Chañaral, or Taltal ($n$ = 11,967).

## Exposure Assessment

Concurrent with other study activities, drinking water samples were obtained from approximately 25 separate sources in each study city. These were drawn from potable water faucets at participating schools, homes of students, and public buildings located near the schools. Water samples (30-mL) were maintained in Teflon-coated bottles on ice and transported to the Montgomery Watson Laboratories (Pasadena, CA) for analysis of perchlorate concentration. Water samples were labeled with identifier codes to conceal city of origin from laboratory personnel.

## Thyroid Assessment in School-Age Children

Also in September 1999, a team of endocrinologists (R.T., C.R., G.G.) examined the thyroid gland of each school-age child for whom informed parental consent was given ($n$ = 163). Goiters were classified on the basis of standardized World Health Organization criteria.[28] The children's height, weight, time of last meal, and general health and nutrition status were ascertained at time of examination. All examiners were blinded to relative perchlorate concentrations in the study cities.

On the same day as the thyroid examination, blood samples were collected from each child between the hours of 9 AM and 3 PM by an experienced nurse using a sterile technique. A blood sample from each child was analyzed on-site for complete blood count by a technician using a portable Coulter counter. A thin smear was prepared for subsequent microscopic analysis by a pathologist at the Catholic University clinical laboratories in Santiago. Frozen serum samples were transported to Catholic University clinical laboratories for analysis of thyroid hormones (TSH, T4, free T4, triiodothyronine), antiperoxidase antibody, liver enzymes (aspartate aminotransferase, lactate dehydrogenase, alkaline phophatase), and tests of kidney function (blood urea nitrogen, serum creatinine).

A first-void spot urine sample (minimum 30 mL) was obtained from each child. These were analyzed for iodine and creatinine content at Catholic University clinical laboratories in Santiago.

## Neonatal Thyroid Assessment

The National Program for Mass Screening of Congenital Hypothyroidism was initiated throughout Chile in 1992. A heel-stick blood sample is obtained from newborns to assess the presence of congenital hypothyroidism. Participation is mandatory, and follow-up for treatment

after diagnosis is supervised by the Ministry of Health. All laboratory analyses for the National Program for Mass Screening of Congenital Hypothyroidism in Chile are conducted in the San Juan de Dios Hospital Laboratory in Santiago.

Neonatal TSH level, sex, date of birth, and date of screening were obtained for all neonates born between February 1996 and January 1999 and whose city of origin was Antofagasta, Chañaral, or Taltal ($n$ = 11,967). A systematic laboratory error (gamma counter contamination) occurred between December 1, 1997 and June 30, 1998, which caused TSH to be reported very low (0.1 μU/mL) for a high proportion (29.1%) of blood samples analyzed. The error was limited to this 7-month period and affected a similar proportion of samples from each city (18.6% from Antofagasta, 16.6% from Chañaral, 12.8% from Taltal). All data obtained during the 7-month period in question were excluded from the present study, leaving 9784 neonatal records for analysis.

## Statistical Methods

Mean perchlorate concentrations in drinking water were determined for Antofagasta, Chañaral, and Taltal on the basis of 25 water samples collected in each city. The analysis of school-age children excluded one child from Taltal who had autoimmune hypothyroidism (anti-thyroid antibody titer, 1:25,000; TSH, 34 μ/mL). Analyses were conducted for children who lived in the city at time of examination ($n$ = 162), and for children who had lived in their city continuously since birth and whose mother had lived there for the year preceding their birth ($n$ = 127). The latter group was assumed to be exposed to a relatively constant concentration of perchlorate from conception to time of examination.

Linear regression was used to compare TSH levels (and free T4 levels) in schoolchildren by city of residence. Because Antofagasta has non-detectable perchlorate in drinking water, it was used as the reference city for comparisons with Chañaral (low exposure) and Taltal (highest exposure). These analyses were adjusted for potential confounding by age (continuous linear variable centered around the mode, 7 years), sex (female, 0; male, 1), and urinary iodine excretion (continuous linear variable centered around the mean, 72 μg/dL). Logistic regression was used to estimate relative risk of goiter (and of family history of thyroid disease) associated with city of residence while adjusting for age, sex, and urinary iodine excretion.

**TABLE 1**
Perchlorate Concentrations (μg/L) in Drinking Water From Select Cities in Chile

| City | $n$ | Mean | SD | Min | Max |
|---|---|---|---|---|---|
| Antofagasta | 25 | ND* | - | ND | ND |
| Chañaral† | 25 | 5.5 | 1.6 | ND | 6.7 |
| Taltal | 25 | 111.6 | 6.7 | 100 | 120 |

* ND, non-detectable (<4.0 μg/L, the minimum reporting limit).
† Four of 25 samples from Chañaral were ND and for computing the mean were assumed to have a concentration of 2.0 μg/L.

**TABLE 2**
Characteristics of All Schoolchildren by City (Means ± SD,* or % Where Indicated)

| Data | Antofagasta ($n$ = 53) | Chañaral ($n$ = 49) | Taltal ($n$ = 60)† |
|---|---|---|---|
| Personal | | | |
| Age (y) | 7.2 ± 0.3 | 7.3 ± 0.6 | 7.4 ± 0.6 |
| Sex (% male) | 50.9 | 57.1 | 46.7 |
| Height (cm) | 124.6 ± 7.2 | 122.8 ± 6.8 | 123.2 ± 6.1 |
| Weight (kg) | 25.4 ± 5.4 | 25.6 ± 7.5 | 27.5 ± 5.5 |
| History of breastfeeding (%) | 84.9 | 85.7 | 73.3 |
| Lifelong residence in city (%) | 67.9 | 83.7 | 83.3 |
| Thyroid | | | |
| TSH (μU/mL) | 3.3 ± 1.8 | 2.9 ± 1.3 | 3.0 ± 1.4 |
| T4 (μg/dL) | 9.1 ± 1.3 | 10.4 ± 1.4 | 9.3 ± 1.2 |
| Free T4 (ng/dL) | 1.2 ± 0.1 | 1.3 ± 0.1 | 1.4 ± 0.2 |
| T3 (ng/dL) | 208.6 ± 29.7 | 211.0 ± 20.9 | 212.0 ± 21.9 |
| Goiter (% with) | 17.0 | 26.5 | 23.3 |
| Family history of thyroid disease (%)‡ | 13.2 | 10.2 | 30.0 |
| Other laboratory | | | |
| Leukocytes ($\times 10^3$) | 7.9 ± 1.9 | 7.7 ± 1.5 | 8.4 ± 2.1 |
| Hemoglobin (g/dL) | 12.2 ± 0.8 | 12.3 ± 0.8 | 12.1 ± 0.8 |
| Hematocrit (%) | 36.8 ± 2.2 | 36.9 ± 2.1 | 36.3 ± 2.4 |
| Aspartate aminotransferase (U/L) | 30.4 ± 5.4 | 30.6 ± 9.1 | 29.2 ± 4.8 |
| Lactate dehydrogenase (U/L) | 219.4 ± 30.7 | 207.3 ± 30.4 | 195.1 ± 29.2 |
| Alkaline phosphatase (U/L) | 303.1 ± 65.3 | 314.1 ± 73.2 | 292.1 ± 66.7 |
| Total bilirubin (mg/dL) | 0.3 ± 0.2 | 0.4 ± 0.5 | 0.2 ± 0.1 |
| Creatinine (mg/dL) | 0.6 ± 0.06 | 0.6 ± 0.05 | 0.6 ± 0.07 |
| Blood urea nitrogen (mg/dL) | 11.5 ± 2.9 | 12.5 ± 3.1 | 12.8 ± 3.2 |
| Glucose (mg/dL) | 92.3 ± 10.0 | 90.4 ± 7.8 | 95.5 ± 9.1 |
| Urine iodine (μg/dL) | 75.6 ± 40.4 | 61.4 ± 35.7 | 76.6 ± 47.4 |
| Urine creatinine (mg/dL) | 0.09 ± 0.14 | 0.09 ± 0.02 | 0.08 ± 0.03 |
| Urine I/creatinine (μg/g) | 1057.2 ± 377.9 | 827.2 ± 359.4 | 947.4 ± 364.2 |

* SD, standard deviation; TSH, thyroid-stimulating hormone; T4, thyroxine; T3, triiodothyronine.
† Excluded one child with evidence of autoimmune hypothyroidism (antiperoxidase antibody titer, 1:25,000; TSH, 34 μU/ml).
‡ Direct relative (parent, sibling, grandparent, great-grandparent, aunt, uncle, or cousin) with history of goiter, hypothyroidism, or subtotal thyroidectomy.

TABLE 3
Characteristics of Schoolchildren With Lifelong Residence in Their Respective City (Means ± SD, or % Where Indicated)*

| Data | Antofagasta ($n$ = 36) | Chañaral ($n$ = 41) | Taltal ($n$ = 50)† |
|---|---|---|---|
| Personal | | | |
| Age (y) | 7.1 ± 0.2 | 7.3 ± 0.6 | 7.4 ± 0.6 |
| Sex (% male) | 55.6 | 63.4 | 50.0 |
| Height (cm) | 125.3 ± 8.2 | 122.0 ± 6.5 | 123.4 ± 6.4 |
| Weight (kg) | 25.5 ± 4.7 | 25.3 ± 7.6 | 28.0 ± 5.8 |
| History of breastfeeding (%) | 80.6 | 85.4 | 72.0 |
| Thyroid | | | |
| TSH (μU/mL) | 3.1 ± 1.2 | 2.9 ± 1.3 | 3.0 ± 1.3 |
| T4 (μg/dL) | 9.0 ± 1.4 | 10.3 ± 1.3 | 9.3 ± 1.1 |
| Free T4 (ng/dL) | 1.2 ± 0.1 | 1.3 ± 0.1 | 1.4 ± 0.1 |
| T3 (ng/dL) | 209.7 ± 30.9 | 211.5 ± 20.8 | 212.4 ± 22.2 |
| Goiter (% with) | 22.2 | 19.5 | 26.0 |
| Family history of thyroid disease (%)‡ | 11.1 | 9.8 | 30.0 |
| Other laboratory | | | |
| Leukocytes ($\times 10^3$) | 8.0 ± 2.1 | 7.8 ± 1.6 | 8.4 ± 1.9 |
| Hemoglobin (g/dL) | 12.2 ± 0.7 | 12.2 ± 0.8 | 12.1 ± 0.9 |
| Hematocrit (%) | 36.6 ± 2.0 | 36.8 ± 2.2 | 36.4 ± 2.5 |
| Aspartate aminotransferase (U/L) | 30.8 ± 5.7 | 31.4 ± 9.7 | 29.6 ± 4.6 |
| Lactate dehydrogenase (U/L) | 221.0 ± 33.4 | 206.5 ± 32.1 | 195.4 ± 28.4 |
| Alkaline phosphatase (U/L) | 308.9 ± 70.7 | 308.8 ± 58.5 | 289.3 ± 67.6 |
| Total bilirubin (mg/dL) | 0.3 ± 0.2 | 0.3 ± 0.1 | 0.2 ± 0.1 |
| Creatinine (mg/dL) | 0.6 ± 0.06 | 0.6 ± 0.05 | 0.6 ± 0.07 |
| Blood urea nitrogen (mg/dL) | 11.1 ± 2.7 | 12.6 ± 3.1 | 13.0 ± 3.1 |
| Glucose (mg/dL) | 93.9 ± 10.0 | 90.4 ± 8.4 | 96.1 ± 9.0 |
| Urine iodine (μg/dL) | 77.5 ± 38.4 | 61.6 ± 34.2 | 77.3 ± 49.5 |
| Urine creatinine (mg/dL) | 0.07 ± 0.03 | 0.09 ± 0.11 | 0.08 ± 0.03 |
| Urine I/creatinine (μg/g) | 1096.4 ± 407.6 | 862.2 ± 375.1 | 962.8 ± 370.0 |

* For definition of abbreviations, see Table 2.
† Excluded one child with evidence of autoimmune hypothyroidism (antiperoxidase antibody titer, 1:25,000; TSH, 34 μU/ml).
‡ Direct relative (parent, sibling, grandparent, great-grandparent, aunt, uncle, or cousin) with history of goiter, hypothyroidism, or subtotal thyroidectomy.

Statistical power of the schoolchildren analysis was estimated assuming that the TSH mean for children without exposure to perchlorate is 3.0 μU/mL (standard deviation [SD] 1.5 μU/mL) and the free T4 mean for children without exposure to perchlorate is 1.3 ng/dL (SD 0.2 ng/dL). The study had greater than 90% power to detect a 1-μU/mL difference in average TSH, or a 0.5-ng/dL difference in average free T4, when comparing Antofagasta with either of the exposed cities.

In the neonatal analysis, linear regression was used to compare neonatal TSH levels by city of origin while adjusting for potential confounding by sex (female, 0; male, 1) and age (dummy variable using the third day of life as reference). Neonatal TSH levels exhibited some skewness, particularly among newborns originating in Antofagasta. Therefore, a natural logarithmic transformation of neonatal TSH was used to obtain approximately normally distributed data appropriate for linear regression. Model assumptions were evaluated by using diagnostic plots of residuals and normal probability plots. All analyses were performed by using Stata statistical software.[29]

## Results

Taltal had relatively high concentrations of perchlorate in drinking water (mean, 112 μg/L; range, 100 to 120 μg/L). In Chañaral, 4 of 25 water samples were below the minimum reporting limit of 4.0 μg/L; the other 21 samples averaged 6.2 μg/L (range, 5.3 to 6.7 μg/L). Perchlorate was non-detectable (<4.0 μg/L) in all water samples from Antofagasta (Table 1). The difference in average perchlorate concentration between Taltal and either other city, and the difference between that in Chañaral and Antofagasta, was statistically significant ($P < 0.0001$).

### Results in School-Age Children

Table 2 presents characteristics of all schoolchildren after exclusion of one individual with autoimmune hypothyroidism ($n$ = 162). Table 3 presents characteristics only of children who resided continuously in their respective city since conception ($n$ = 127). The children included nearly equal numbers of boys and girls, ages 6 to 8 years. Because perchlorate may be transmitted in breast milk, the children's nutritional history for the first 6 months of life was ascertained from their parents. The proportion of children who were breast-fed was similar among the three cities and ranged from 72% to 86%.

Mean levels of TSH, T4, free T4, and triiodthyronine appeared to be very similar among the three cities (Tables 2 and 3). Among lifelong residents, prevalence of goiter was similar in Taltal (26%) compared with Chañaral (20%) and Antofagasta (22%); ($P$ = 0.46 and $P$ = 0.69, respectively). All goiters observed were grade I except for four grade II goiters (two in Chañaral and one each in Taltal and Antofagasta). Taltal residents were more likely to self-report a family history of thyroid disease, which was defined as having any blood relative with a history of goiter, hypothyroidism, or subtotal thyroidectomy (Taltal 30%, Antofagasta 11%, Chañaral 10%, among lifelong residents). All laboratory measures of bone marrow, liver, and kidney function in the study children were very similar among the three cities.

Linear regression comparisons of TSH by city of residence are shown

**TABLE 4**
Linear Regression Analysis of TSH,* Comparing Schoolchildren in Chañaral and Taltal With Those in Antofagasta†

| | All Residents ($n$ = 162) | | | Lifelong Residents ($n$ = 127) | | |
|---|---|---|---|---|---|---|
| Variable | Coefficient | 95% CI | $P$ Value | Coefficient | 95% CI | $P$ Value |
| Antofagasta | 3.42 | 2.93–3.92 | – | 3.11 | 2.61–3.61 | – |
| Chañaral | −0.37 | −0.98–0.24 | 0.24 | −0.09 | −0.68–0.50 | 0.76 |
| Taltal | −0.37 | −0.95–0.21 | 0.21 | −0.13 | −0.70–0.43 | 0.64 |
| Age (y) | 0.21 | −0.26–0.68 | 0.38 | 0.21 | −0.22–0.64 | 0.34 |
| Sex (male) | −0.35 | −0.83–0.14 | 0.16 | −0.23 | −0.70–0.23 | 0.33 |
| Iodine (μg/dL) | 0.002 | −0.004–0.008 | 0.51 | 0.003 | −0.003–−0.008 | 0.31 |

* TSH, thyroid-stimulating hormone; CI, confidence interval.
† Adjusted for age (centered around 7 years), sex (female, 0; male, 1), and urinary iodine (centered around the mean); excluded one child with autoimmune hypothyroidism.

**TABLE 5**
Linear Regression Analysis of Free T4,* Comparing Schoolchildren in Chañaral and Taltal With Those in Antofagasta†

| | All Residents ($n$ = 162) | | | Lifelong Residents ($n$ = 127) | | |
|---|---|---|---|---|---|---|
| Variable | Coefficient | 95% CI | $P$ Value | Coefficient | 95% CI | $P$ Value |
| Antofagasta | 1.24 | 1.19–1.28 | – | 1.25 | 1.19–1.31 | – |
| Chañaral | 0.09 | 0.03–0.14 | 0.003 | 0.09 | 0.02–0.15 | 0.01 |
| Taltal | 0.14 | 0.09–0.19 | <0.001 | 0.15 | 0.09–0.22 | <0.001 |
| Age (y) | 0.007 | −0.04–0.05 | 0.74 | 0.01 | −0.03–0.06 | 0.57 |
| Sex (male) | −0.03 | −0.08–0.01 | 0.17 | −0.06 | −0.11–−0.004 | 0.04 |
| Iodine (μg/dL) | −0.00002 | −0.0006–0.0005 | 0.95 | <0.00001 | −0.0006–0.0006 | 0.99 |

* Free T4, free thyroxine; CI, confidence interval.
† Adjusted for age (centered around 7 years), sex (female, 0; male, 1), and urinary iodine (centered around the mean); excluded one child with autoimmune hypothyroidism.

in Table 4. Adjusted for age, sex, and urinary iodine excretion, average TSH was slightly lower among Chañaral and Taltal children compared with Antofagasta children, but this was not statistically significant, whether based on all children ($P > 0.2$) or lifelong residents ($P > 0.6$).

Comparisons of free T4 by city of residence are shown in Table 5. Adjusted for the same factors, average free T4 was higher among Chañaral and Taltal children compared with Antofagasta children, and these differences were highly significant whether based on all children or lifelong residents ($P \leq 0.01$ for Chañaral, $P < 0.001$ for Taltal). With the particular coding of variables that was used (see Table 5 footnote), the coefficient for lifelong residents of Taltal (0.15) may be interpreted as follows: Among 7-year-old girls with average urinary iodine excretion, average free T4 in Taltal was 0.15 ng/dL greater than that in Antofagasta, and this difference did not seem to be consistent with chance ($P < 0.001$). Diagnostic residual plots and normal probability plots revealed no substantial departures from linear regression assumptions.

**TABLE 6**
Odds Ratios for Association Between Goiter in Schoolchildren and City of Residence*

| | All Residents ($n$ = 162) | | Lifelong Residents ($n$ = 127) | |
|---|---|---|---|---|
| City | Odds Ratio | 95% CI† | Odds Ratio | 95% CI |
| Antofagasta | 1.00 | – | 1.00 | – |
| Chañaral | 1.96 | 0.70–5.45 | 1.03 | 0.32–3.29 |
| Taltal | 1.43 | 0.54–3.80 | 1.11 | 0.38–3.24 |

* Adjusted for age, sex, and urinary iodine; excluded one child with autoimmune hypothyroidism.
† CI, confidence interval.

Table 6 shows the estimated relative risk of goiter for children in Chañaral and Taltal compared with that of children in Antofagasta, adjusted for age, sex, and urinary iodine. In the analysis of all study

**TABLE 7**
Odds Ratios for Association Between Self-Reported Family History of Thyroid Disease* Among Schoolchildren and City of Residence†

| | All Residents ($n$ = 162) | | Lifelong Residents ($n$ = 127) | |
|---|---|---|---|---|
| City | Odds Ratio | 95% CI‡ | Odds Ratio | 95% CI |
| Antofagasta | 1.00 | - | 1.00 | - |
| Chañaral | 0.89 | 0.25–3.19 | 1.04 | 0.21–5.09 |
| Taltal | 3.35 | 1.19–9.38 | 4.97 | 1.29–19.17 |

* Direct relative (parent, sibling, grandparent, great-grandparent, aunt, uncle, or cousin) with history of goiter, hypothyroidism, or subtotal thyroidectomy.
† Adjusted for age, sex, and urinary iodine; excluded one child with autoimmune hypothyroidism.
‡ CI, confidence interval.

**TABLE 8**
Neonatal Characteristics in Select Cities in Chile

| | Antofagasta ($n$ = 8888; 51.8% male) | | Chañaral ($n$ = 468; 49.5% male) | | Taltal ($n$ = 428; 50.7% male) | |
|---|---|---|---|---|---|---|
| | Mean ± SD* | Median | Mean ± SD | Median | Mean ± SD | Median |
| Age at screening (day of life) | 4.1 ± 3.7 | 3 | 4.9 ± 4.6 | 4 | 6.6 ± 4.4 | 6 |
| TSH (μU/mL) | | | | | | |
| Total | 3.4 ± 7.8 | 2.6 | 3.0 ± 2.5 | 2.3 | 2.4 ± 1.9 | 2.0 |
| Male | 3.6 ± 6.1 | 2.8 | 3.4 ± 2.7 | 2.6 | 2.5 ± 2.1 | 2.1 |
| Female | 3.2 ± 7.4 | 2.4 | 2.6 ± 2.2 | 2.0 | 2.2 ± 1.7 | 1.9 |
| Day 1–2 ($n$ = 63) | 3.2 ± 1.9 | 2.7 | 3.2 ± 3.5 | 1.9 | 4.2 ± 1.2 | 4.2 |
| Day 3 ($n$ = 6914) | 3.7 ± 7.0 | 2.8 | 3.1 ± 2.2 | 2.4 | 3.3 ± 2.4 | 2.5 |
| Day 4 ($n$ = 1257) | 3.3 ± 14.4 | 2.2 | 3.2 ± 2.7 | 2.3 | 2.1 ± 1.8 | 1.9 |
| Day 5 ($n$ = 282) | 2.3 ± 1.6 | 1.9 | 3.1 ± 2.8 | 2.4 | 2.2 ± 1.7 | 2.0 |
| Day 6 ($n$ = 215) | 2.4 ± 1.9 | 1.9 | 2.6 ± 2.1 | 2.0 | 2.2 ± 1.7 | 1.7 |
| Day 7+ ($n$ = 921) | 2.4 ± 2.0 | 1.9 | 2.1 ± 1.4 | 1.7 | 2.1 ± 1.7 | 1.8 |

* SD, standard deviation; TSH, thyroid-stimulating hormone.

children, there was a small, nonsignificant increased risk of goiter in Chañaral and Taltal compared with Antofagasta. Among lifelong residents, however, there was virtually no difference in risk of goiter among the three cities.

Table 7 presents logistic regression results for self-reported family history of thyroid disease. Adjusted for age, sex, and urinary iodine, lifelong residents of Taltal were 5 times more likely to report a family history of thyroid disease compared with lifelong residents of Antofagasta (95% confidence interval, 1.3 to 19.2). Chañaral children had no increased prevalence of self-reported family history of thyroid disease.

Other than slight confounding in a few analyses by sex, which was controlled for, there was no appreciable confounding evident by age, urinary iodine, or any other variables listed in Tables 2 and 3. Iodine excretion was considered to be a potential confounder to the extent that iodine intake may be associated with perchlorate exposure levels. However, no evidence was found that urinary iodine levels were associated with either city of residence or thyroid function indices.

## Neonatal Results

From 1992 to 1999, 222 cases of congenital hypothyroidism were detected in Chile out of 773,440 newborns screened, corresponding to an incidence rate of 1 per 3484 newborns screened (Internal Report, National Program for Mass Screening of Congenital Hypothyroidism and Phenylketonuria, Ministry of Health, Chile; unpublished). Among newborns analyzed in the present study, seven presumptive cases of congenital hypothyroidism (TSH ≥ 25 μU/mL) were detected, all originating in Antofagasta, corresponding to an incidence rate in Antofagasta of 1 per 1270 newborns. Maximum TSH levels observed in Chañaral and Taltal were 17.1 μU/mL and 13.5 μU/mL, respectively.

Neonatal characteristics are presented by study city in Table 8. Average TSH seemed to be lower in Taltal (2.4 μU/mL) than in Antofagasta (3.4 μU/mL) or in Chañaral (3.0 μU/mL). Boys had a higher average TSH than girls in each city (formally tested below). In Antofagasta, over half of all newborns were screened on the third day of life. Median age at time of screening was 4 days in Chañaral and 6 days in Taltal. TSH levels seemed to peak on day 2 or 3 and to decline somewhat afterward (Table 8).

Linear regression comparisons of log TSH by city are shown in Table 9. Adjusted for sex and age, average log TSH in Taltal was significantly lower compared with Antofagasta ($P < 0.001$) or Chañaral ($P < 0.001$, not shown); there was no significant difference in average log TSH between Chañaral and Antofagasta. With the coding of variables that was used, the coefficient for Taltal in Table 9 (-0.25) may be interpreted in this way: Median TSH for 3-day-old girls in Taltal was $(1 - e^{-0.25})$ 22% lower than that of 3-day-old girls in Antofagasta, and this difference did not seem to be consistent with chance ($P < 0.001$).

The small amount of confounding identified in these analyses was almost entirely owing to age at time of screening. Sex and age were both significant predictors of TSH. Adjusted for city and age, boys had higher TSH than girls ($P < 0.001$). TSH levels were significantly lower at age 4 days of life or greater compared with day 3 ($P < 0.001$). Diagnostic residual plots and normal probability plots suggested good

TABLE 9
Linear Regression of Neonatal Log TSH* in Chañaral and Taltal Compared With That in Antofagasta

| | Unadjusted | | | Adjusted† | | |
|---|---|---|---|---|---|---|
| Variable | Coefficient | 95% CI | *P* Value | Coefficient | 95% CI | *P* Value |
| Antofagasta | 0.91 | 0.90–0.93 | - | 0.91 | 0.89–0.94 | - |
| Chañaral | −0.10 | −0.18–−0.03 | 0.008 | 0.003 | −0.08–0.08 | 0.94 |
| Taltal | −0.46 | −0.54–−0.38 | <0.001 | −0.25 | −0.34–−0.17 | <0.001 |
| Sex (male) | | | | 0.15 | 0.11–0.18 | <0.001 |
| Age (days) | | | | | | |
| 1–2 | | | | −0.004 | −0.21–0.20 | 0.97 |
| 3 | | | | - | - | - |
| 4 | | | | −0.24 | −0.29–−0.19 | <0.001 |
| 5 | | | | −0.33 | −0.42–−0.23 | <0.001 |
| 6 | | | | −0.35 | −0.46–−0.24 | <0.001 |
| 7+ | | | | −0.40 | −0.46–−0.35 | <0.001 |

* TSH, thyroid-stimulating hormone; CI, confidence interval.
† Adjusted for sex (female, 0; male, 1) and age (dummy variable using third day of life as reference).

agreement with linear regression assumptions.

## Discussion

Northern Chile is an ideal setting in which to study the effects of perchlorate in drinking water on thyroid function in presumed sensitive subpopulations. The city of Taltal has high concentrations of perchlorate in drinking water (>100 μg/L) compared with most areas of the United States, and it has had a consistent source of water from the same wells since at least 1970. Chañaral and Antofagasta have low and nondetectable perchlorate concentrations, respectively, and because of their proximity and similarity to Taltal were suitable for comparison of populations. School-age children from each of these cities demonstrated evidence of normal dietary iodine ingestion on the basis of median urinary iodine concentrations greater than 50 μg/dL.

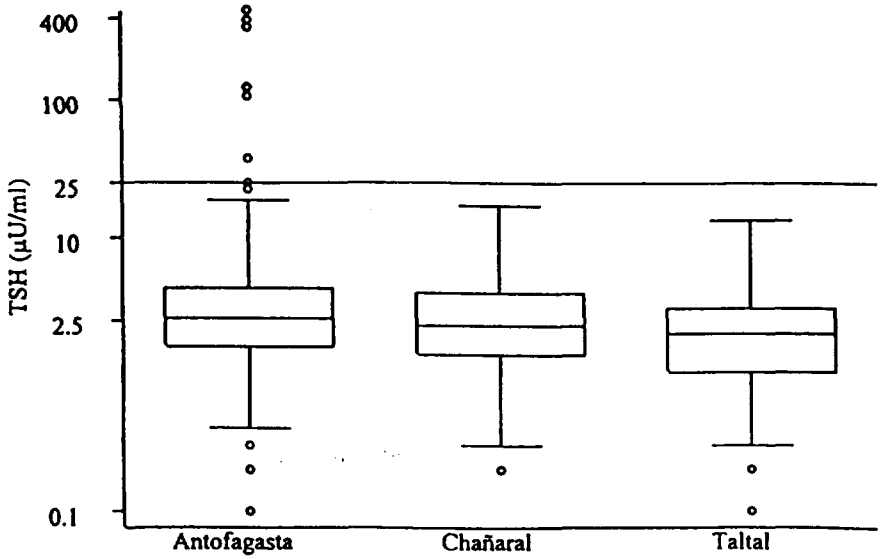


Fig. 2. Neonatal TSH (μU/mL) distribution in select cities in Chile, plotted on natural logarithmic scale. Center lines of boxes represent medians; upper and lower borders of boxes represent the 75th and 25th percentiles, respectively.

This study found no evidence that perchlorate in drinking water at concentrations as high as 120 μg/L suppresses thyroid function in newborns or school-age children. This is the first epidemiological investigation of the potential effects of lifelong perchlorate exposure in school-age children. No clinically or statistically significant difference in TSH levels was found in schoolchildren among the three study cities. Free T4 levels were slightly higher among children who were lifelong residents of Taltal and Chañaral compared with Antofagasta ($P < 0.001$ and $P = 0.01$, respectively). However, the observed differences did not seem to be clinically significant in magnitude and were the opposite of known pharmacological effects of perchlorate. Prevalence of goiter in the children examined was similar among the three cities. No evidence was found of perchlorate-related effects on bone marrow, liver, or kidney function.

Residents of Taltal were more likely to self-report a family history of thyroid disease. Adjusted for age, sex, and urinary iodine, Taltal families were five times more likely to report a history of thyroid disease than Antofagasta families (Table 7). Families of 19 out of 61 (31%) children in Taltal reported having some history of thyroid disease. Twelve of these families reported having a single relative (usually a mother or grandmother) with goiter, hypothyroidism, or unspecified thyroid disease; seven reported having two or more relatives with goiter, hypothyroidism, or other thyroid disease (two of these families had a history of hyperthyroidism). Not all of these family histories have been verified, and reasons for them are as yet unknown. Because family history was self-reported by parents, reporting bias may have occurred if Taltal residents had a heightened suspicion of thyroid problems compared with residents of Chañaral or Antofagasta. Alternatively, these findings may reflect a change in exposure patterns

over the past several generations. Because iodized salt was not introduced in the region until 1982, it is possible that a combination of low iodine intake and the perchlorate concentrations in Taltal was sufficient to cause thyroid problems in past decades. Further investigation will be needed to clarify these family history findings and to evaluate possible relationships between perchlorate exposure in Taltal and thyroid function in adults.

No cases of congenital hypothyroidism were detected in cities with detectable perchlorate in drinking water (Taltal and Chañaral). Neonatal TSH levels were slightly lower in Taltal (highest exposure) compared with those of the other cities studied ($P < 0.001$); this was in opposition to the known pharmacological effects of perchlorate. The magnitude of observed TSH differences among study cities did not seem to be clinically significant (Fig. 2). A separate analysis (not shown) was conducted without exclusion of neonatal data obtained during the period affected by laboratory error. TSH comparisons showed the same relationships among study cities as indicated in the reported analysis. Details of this secondary analysis are available from the authors upon request.

A small proportion of Antofagasta neonatal records may have come from newborns originating from small villages surrounding Antofagasta. To assess further the suitability of Antofagasta as a control city, a separate analysis (not shown) was conducted that included a representative sample of newborns originating in Santiago ($n = 12,497$). Santiago had non-detectable perchlorate (<4 μg/L) in all but one of 25 samples of municipal drinking water; the only positive sample had a perchlorate concentration of 7 μg/L. Neonatal TSH levels were similar between Antofagasta (mean ± SD, 3.4 ± 7.8 μU/mL) and Santiago (mean ± SD, 3.4 ± 4.5 μU/mL), and the use of Santiago as an alternate control city gave very similar results to those of the primary analysis. More information about the Santiago neonatal data is available from the authors upon request.

The US Environmental Protection Agency and a number of state health departments are currently attempting to assess the potential magnitude of risk associated with various concentrations of perchlorate in drinking water. This study provides valuable information for the assessment of such risks. It is the first to investigate effects of lifelong exposure to perchlorate at low (5 to 7 μg/L) and relatively high (100 to 120 μg/L) concentrations in drinking water on thyroid function in school-age children, a subpopulation presumed to be sensitive. Perchlorate concentrations currently detected in some water sources for southern California and southern Nevada are in the range of 5 to 8 μg/L and up to 15 μg/L, respectively.[3] These concentrations are comparable with those detected in Chañaral (5 to 7 μg/L), whereas Taltal has perchlorate concentrations more than 10 times greater from sources that have been used continuously for 30 years.

This study is the third epidemiological investigation of the effects of perchlorate in drinking water on neonatal thyroid function, and the first to investigate perchlorate concentrations as high as or exceeding 100 μg/L. The first two studies of perchlorate and neonatal thyroid function were conducted in California and Nevada.[8,9] These studies found no increased incidence of congenital hypothyroidism[8] or decreased T4 levels[9] associated with currently detected perchlorate concentrations. These findings and those of the present study are consistent with two occupational studies[6,7] that found no adverse health effects due to chronic respiratory perchlorate exposure to healthy adults.

In summary, 162 school-age children and 9784 newborns in northern Chile were studied for potential adverse effects of perchlorate in drinking water at concentrations comparable with those detected in Lake Mead and the downstream Colorado River (5 to 8 μg/L) and at considerably higher concentrations (100 to 120 μg/L). No evidence was found that perchlorate in drinking water at these concentrations is associated with thyroid suppression in newborns or school-age children. Among school-age children, no evidence was found of adverse effects on thyroid, bone marrow, liver, or kidney function.

## Acknowledgment

The authors thank Mrs Sol Perez and Mrs Carolina Uribe for their assistance in obtaining blood samples from children and processing them on-site in northern Chile; Dr Nancy Vivanco, Mr Bernardo Bruggendieck, and Mrs Ines Lopez Ortiz for their contributions in obtaining neonatal thyroid data in Chile; and Mrs Carolyn Childress for her assistance with data entry. They also thank Dr Luis Rodriguez of the Catholic University clinical laboratories (Santiago, Chile) for his help in conducting thyroid and chemistry assays, and Montgomery Watson Laboratories (Pasadena, Calif.) for analyzing perchlorate in drinking water samples. Funding for this study was provided by Kerr-McGee Chemical LLC, Oklahoma City, Okla

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